FACILE SYNTHESIS OF 2-AMINO-DIHYDRO-4(1H)-PYRIMIDINONE DERIVATIVES: CYCLIZATION OF N-SUBSTITUTED GUANIDINES WITH α,β-UNSATURATED ESTERS

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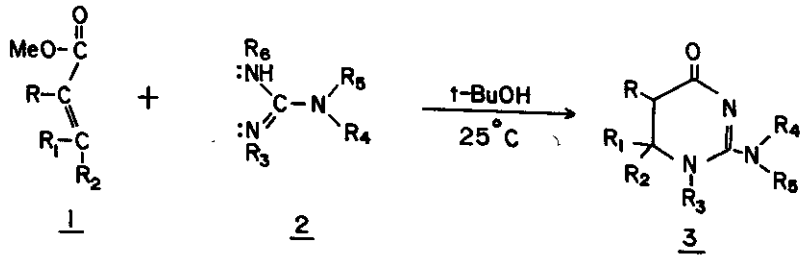
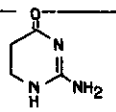
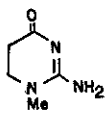
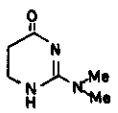
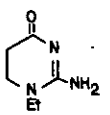
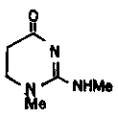
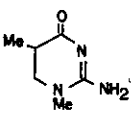
Abstract - 2-Amino-5,6-dihydropyrimidin-(1H)-4-one derivatives containing guanidine moiety (3) have been synthesized in excellent yields by the cyclization of free N-substituted guanidines with α,β-unsaturated esters such as methyl acrylate and methyl methacrylate derivatives under mild conditions.

Naturally occurring heterocycles possessing guanidine skeletones have been widely found in such biologically active compounds as viomycidine[1], tuberactidine[2], tetrodotoxin[3] and saxitoxin[4]. Dihydropyrimidines containing a guanidine moiety[5] have been demonstrated to have a selectivity for the sodium channel in the muscle membrane qualitatively similar to that from tetrodotoxin[3] or saxitoxin[4] and also reported to be important intermediates in the catabolism and anabolism of pyrimidines[6]. The cyclization of α,β-unsaturated carboxylic acids with amidines has been known to produce dihydropyrimidine derivatives in low yields by acid catalized ring formation under reflux conditions[7]. This methed has been rather widely employed, but requires high reaction temperature in acidic condition. Consequently, the yields are poor due to the unstability of the products[8] and the formation of side products. While, catalytic hydrogenation of 4-pyrimidinones has been known to yield dihydropyrimidines usaully in low yields due to the difficulty to control the degree of hydrogenation and to the formation of side products[9]. We describe herein an efficient synthesis of 5,6-dihydropyrimidin-(1H)-4-ones (3) by a simple cyclization of free N-alkylguanidines (2) with α,β-unsaturated esters (1) in tertiary butanol or in isopropanol at room temperature.



1 2 3

Table I. cyclization of Guanidine Derivatives with α,β-Unsaturated Esters at 25°C

Run	Substrates	Reaction Time (h)	Products	Yields[a](%)
1	R=R_1=R_2=R_3=R_4=R_5=R_6=H	4.0	 4	97
2	R=R_1=R_2=R_4=R_5=R_6=H R_3=Me	3.0	 5	100
3	R=R_1=R_2=R_5=R_6=H R_4=R_5=Me	48	 6	100
4	R=R_1=R_2=R_4=R_5=R_6=H R_3=Et	3.5	 7	99
5	R=R_1=R_2=R_5=R_6=H R_3=R_4=Me	48	 8	70
6	R=R_3=Me, R_1=R_2=R_4=R_5=R_6=H	24	 9	70
7	R=R_1=R_2=R_5=R_6=H R_3=R_4=R_6=Me	48	no reaction[b]	
8	R=R_4=R_5=H R_1=R_2=R_3=R_6=Me	48	no reaction[b]	

a) Isolated yields, b) Starting materials were recovered quantitatively.

4: mp 253-55°C, ^{1}H nmr(D_2O-HCl) δ2.90(2H, t, J=6.99 Hz), 3.87 2H, t, J=6.99 Hz). UV λ_{max}^{MeOH} nm (ε), 225(8.27x10^3), 251(5.117x10^3); H_2O(pH 12) 210(6.871x10^3), 238(7.016x10^3). ir(KBr)cm^{-1}, 3360, 3100, 1670, 1600, 1570, 1480, 1420, 1400, 1340, 1195 (>m).

5: mp 255-57°C, ^{1}H nmr(D_2O) δ2.20(2H, t, J=6.99 Hz), 2.83(3H, s, N-Me), 3.25(2H, t, -N-CH_2-). UV λ_{max}^{MeOH} nm (ε), 205(1.41x10^4), 240(1.393x10^4); H_2O(pH 12) 207(1.333x10^4), 238 (1.212x10^4).

6: mp 169-71°C, ^{1}H nmr(D_2O) δ2.22(2H, t, J=6.41 Hz), 2.83(6H, s), 3.20(2H, t, J=6.41 Hz). UV λ_{max}^{MeOH} nm (ε) 236(1.44x10^4), H_2O(pH 12) 232(1.35x10^4).

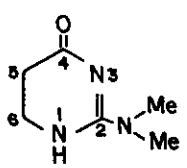
7: mp 249-51°C(dec.), ^{1}H nmr(D_2O) δ1.16(3H, t, J=7.99 Hz), 2.50(2H, t, J=7.80 Hz), 3.37(2H, q, J=7.99 Hz), 3.47(2H, t, J=7.80 Hz), UV λ_{max}^{MeOH} nm (ε) 206 (1.325x10^4), 240 (1.282x10^4), H_2O(pH 12) 208(1.222x10^4), 238(1.085x10^4)

8: mp 170-174°C, ^{1}H nmr(D_2O) δ2.50(2H, t, J=6.99 Hz), 2.82(3H, s, NH Me), 2.97(3H, s, N-Me), 3.47(2H, t, J=6.99 Hz). UV λ_{max}^{MeOH} nm (ε) 220(1.123x10^4), 238(1.063x10^4), H_2O(pH 12) 219(1.052x10^4), 236(7.478x10^3).

9: mp 239-41°C, ^{1}H nmr(D_2O) δ1.00(3H, d, J=6.99 Hz), 2.43(1H, m), 2.92(3H, s, -N-Me), 3.15(1H, d, J=12 Hz), 3.28(d, 1H, J=12 Hz). λ_{max}^{MeOH} nm (ε) 205(1.146x10^4), 238(1.055x10^4), D_2O(pH 12) 207(1.055x10^4) 236(9.60x10^3).

In a typical run (Run 3), 1,1-dimethylguanidine sulfate[10] (488 mg, 2 mmol) was suspended in a sodium isopropoxide solution (Na: 110 mg, 4.78 mmole, i-PrOH : 12 ml) under anhydrous helium. After the mixture was refluxed for 1.5 h, the precipitates were removed by filtration to give a free 1,1-dimethylguanidine solution. To the filtrate methyl acrylate (0.35 ml. 4 m mole) was slowly added at 25°C and the reaction mixture was stirred at 25° for ca. 48 h until only one spot of product remained on tlc. (Rf = 0.45, silica-gel: Merch 60 GF 254, solvent: MeOH). The reaction mixture was concentrated under reduced pressure to give the crude product (6) which was purified by a column chromatography (Wako silica gel 100 mesh, solvent: MeOH, yield: 600 mg = 100%, ^{1}H NMR, UV, and IR spectra met 6).

The results obtained are summarized in Table I.



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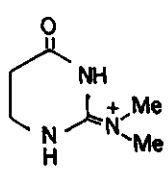
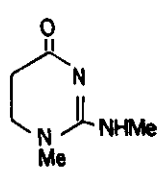


6′



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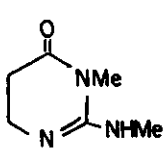

8′

The structure 3 and the structure of the product (6) were assigned on the basis of the data of its UV and ^{1}H nmr spectra. The presence of a conjugated double bond with a carbonyl group in all the products was determined by comparison of UV spectra of the products (4, 5, 7, 8, and 9)

with that of 6 which is a model compound fixed in the 2-amino form and can not exist in the imino form (6') because of the dimethylamino group at the 2-position. The λ_{max} (236 nm[11] in MeOH) and (1.44×10^4) values of 6 are close to those of all the products. If the methyl group is attached on N^3 in 8', the chemical shift of N^3-Me in the nmr spectrum should be in the lower field than that 2.97 ppm in 8 because N^3 is located between carbonyl and inmino group[12].

The cyclization appears to be initiated *via* Michael addition of the guanidines to the double bond and then to complete the cyclization with the ester moiety. It is noteworthy that the steric effect does not play an important role in the reaction of 1 with guanidine or methyl guanidine, but that in the case of cyclization of 1 with N,N- or N,N'-dimethylguanidine, it is important fact (Run 3 and 5) and N,N',N"-trimethylguanidine does not react with 1 (Run 7). This efficient method for the synthesis of 3 analogues is now in progress for the further synthetic application and scope.

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